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(54) Title: A COMBINATION THERAPY FOR THE TREATMENT OF HEART FAILURE

(57) Abstract: A combination therapy for the treatment of heart failure comprises administering a combination of levosimendan or a pharmaceutically acceptable salt thereof and a beta-adrenergic receptor antagonist to a patient. The combination synergistically reduces mortality in heart failure patients.

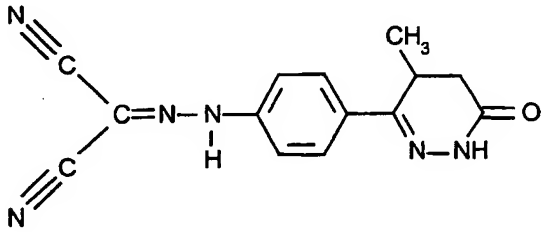
A COMBINATION THERAPY FOR THE TREATMENT OF HEART FAILURE

Technical field

The present invention relates to a method for the treatment of heart failure by administering a synergistic combination of levosimendan or a pharmaceutically acceptable salt thereof and a beta-adrenergic receptor antagonist to a patient in need of such treatment. The invention also relates to a medical product comprising levosimendan or a pharmaceutically acceptable salt thereof and a beta-adrenergic receptor antagonist as a combined preparation.

Background of the invention

Levosimendan, which is the (-)-enantiomer of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile, and the method for its preparation is described in EP 565546 B1. Levosimendan is potent in the treatment of heart failure and has significant calcium dependent binding to troponin. Levosimendan is represented by the formula:



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The hemodynamic effects of levosimendan in man are described in Sundberg, S. et al., Am. J. Cardiol., 1995; 75: 1061-1066 and in Lilleberg, J. et al., J. Cardiovasc. Pharmacol., 26(Suppl.1), S63-S69, 1995. Pharmacokinetics of levosimendan in man after i.v. and oral dosing is described in Sandell, E.-P. et al., J. Cardiovasc. Pharmacol., 26(Suppl.1), S57-S62, 1995. The use of levosimendan in the treatment of myocardial ischemia is described in WO 93/21921. The use of levosimendan in the treatment of pulmonary hypertension is described in WO 99/66912. Clinical studies have confirmed the beneficial effects of levosimendan in congestive heart failure patients.

A method for treating heart failure by administering an inotropic phosphoesterase inhibitor such as enoximone or vesnarinone together with a beta-adrenergic receptor antagonist is described in patent publication WO 98/58638.

Summary of the invention

It has now been found that administration of levosimendan together with a beta-adrenergic receptor antagonist, has a beneficial synergistic effect on the mortality as well as the hemodynamic function of congestive heart failure patients. Therefore, the combination is particularly useful for the treatment of heart failure, including acute and chronic heart failure.

Thus, in one aspect the present invention provides a method for the treatment of heart failure, said method comprising administering to a patient in need thereof levosimendan or a pharmaceutically acceptable salt thereof in combination with a beta-adrenergic receptor antagonist.

In another aspect the invention provides a method for reducing mortality of heart failure patients, said method comprising administering to a patient in need thereof levosimendan or a pharmaceutically acceptable salt thereof in combination with a beta-adrenergic receptor antagonist.

In another aspect the invention provides a medical product comprising, separately or together, as active ingredients levosimendan or a pharmaceutically acceptable salt thereof and a beta-adrenergic receptor antagonist as a combined preparation.

In another aspect invention provides a pharmaceutical composition comprising as active ingredients levosimendan or a pharmaceutically acceptable salt thereof and a beta-adrenergic receptor antagonist.

In another aspect the invention provides the use of levosimendan or a pharmaceutically acceptable salt thereof and a beta-adrenergic receptor antagonist as active ingredients in the manufacture of a combined preparation for simultaneous, separate or sequential administration.

In still another aspect the invention provides use of levosimendan or a pharmaceutically acceptable salt thereof and a beta-adrenergic receptor antagonist as active ingredients in the manufacture of a medicament for reducing mortality of heart failure patients.

Detailed description

The method of the invention relates to a combination therapy for the treatment of heart failure, particularly reducing mortality of heart failure patients, by administering to a patient in need thereof as active ingredients levosimendan or a pharmaceutically acceptable salt thereof and a beta-adrenergic receptor antagonist.

The active ingredients may be administered simultaneously, separately or sequentially. In particular, the method comprises administering to a patient an amount of active ingredients or combination thereof which is effective to reduce mortality of the patient. Preferably, the method comprises administering to a patient a synergistically effective amount of the combination. The administration routes of the active ingredients include, but are not limited to, enteral, e.g. oral or rectal, or parenteral, e.g. intravenous, intramuscular, intraperitoneal or transdermal. In the treatment of acute heart failure, the active ingredients are preferably administered parenterally, intravenous route being particularly preferred. In the treatment of chronic heart failure, oral route is particularly preferred.

Levosimendan may be administered e.g. intravenously using an infusion rate which is from about 0.01 to 10 μg/kg/min, preferably from about 0.02 to 5 μg/kg/min, typically from about 0.05 to 0.4 μg/kg/min. For an intravenous bolus a suitable dose is in the range from about 1 to 200 μg/kg, preferably from about 2 to 100 μg/kg, typically from about 5 to 30 μg/kg. For the treatment of acute heart failure an intravenous bolus followed by continuous infusion may be needed.

Levosimedan may be administered orally to man in daily dose ranging from about 0.1 to 20 mg, preferably from 0.2 to 15 mg, more preferably from 0.5 to 10 mg, given once a day or divided into several doses a day, depending on the age, body weight and condition of the patient. The effective amount of levosimendan to be administered to a subject depends upon the condition to be treated, the route of administration, age, weight and the condition of the patient.

Various beta-adrenergic receptor antagonists, also called beta-blockers, are currently in clinical use for eliminating the harmful chronic myocardial stimulation which is caused by failing heart. Preferred beta-adrenergic receptor antagonists include metoprolol, carvedilol, atenolol, propranolol, acebutolol, betaxolol, nadolol, talinolol or a pharmaceutically acceptable salt thereof.

Particularly preferred beta-adrenergic receptor antagonists to be used in the present invention are metoprolol and carvedilol or a pharmaceutically acceptable salt thereof.

According to the invention, a beta-adrenergic receptor antagonist may be administered in daily doses, which are clinically accepted for such agents. For example, a suitable daily dose of metoprolol as a tartrate or succinate salt, is about 100 - 200 mg and for carvedilol about 5 - 50 mg depending upon the condition to be treated, the route of administration, age, weight and the condition of the patient.

The combination may be supplemented with one or more other active ingredients.

The active ingredients or the combination thereof may be administered periodically, e.g. weekly or biweekly, or daily or several times a day, depending on the patient's needs.

The active ingredients can be formulated into pharmaceutical dosage forms suitable for the treatment according to the present invention using the principles known in the art. They are given to a patient as such or preferably in combination with suitable pharmaceutical excipients in the form of tablets, dragees, capsules, suppositories, emulsions, suspensions or solutions whereby the contents of the active compound in the formulation is from about 0.5 to 100 % per weight. Choosing suitable ingredients for the composition is a routine for those of ordinary skill in the art. It is evident that suitable carriers, solvents, gel forming ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners, wetting compounds, release controlling components and other ingredients normally used in this field of technology may be also used.

The active ingredients may be formulated in the same pharmaceutical formulation. Alternatively, the active ingredients are formulated as separate pharmaceutical dosage forms. The combination of the two pharmaceutical dosage forms may be packed as a single medical product or kit for use in the method of the invention.

Formulations suitable for intravenous administration such as injection or infusion formulation, comprise sterile isotonic solutions of the active ingredient and vehicle, preferably aqueous solutions. Typically an intravenous infusion solution of levosimendan comprises from about 0.01 to 0.1 mg/ml of levosimendan. Typical intravenous solution of metoprolol comprises about 1 mg/ml of metoprolol. The pharmaceutical formulation may be also in the form of an intravenous infusion concentrate to be diluted with an aqueous vehicle before use. Such concentrate may comprise as a vehicle a pharmaceutically acceptable organic solvent such as dehydrated ethanol.

For oral administration of the active ingredients in tablet form, suitable carriers and excipients include e.g. lactose, corn starch, magnesium stearate, calcium phosphate and talc. For oral administration in capsule form, useful carriers and excipients include e.g. lactose, corn starch, magnesium stearate and talc. For controlled release oral compositions release controlling components can be used. Typical release controlling components include hydrophilic gel forming polymers such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, carboxymethyl celluloses, alginic acid or a mixture thereof; vegetable fats and oils including vegetable solid oils such as hydrogenated soybean oil, hardened castor oil or castor seed oil (sold under trade name Cutina HR), cotton seed oil (sold under the trade names Sterotex or Lubritab) or a mixture thereof; fatty acid esters such as triglycerides of saturated fatty acids or their mixtures e.g. glyceryl tristearates, glyceryl tripalmitates, glyceryl trimyristates, glyceryl tribehenates (sold under the trade name Compritol) and glyceryl palmitostearic acid ester.

Tablets can be prepared by mixing the active ingredient with the carriers and excipients and compressing the powdery mixture into tablets. Capsules can be prepared by mixing the active ingredient with the carriers and excipients and placing the powdery mixture in capsules, e.g. hard gelatin capsules. Typically a tablet or a

capsule comprises from about 0.1 to 10 mg, more typically 0.2 to 5 mg, of levosimendan or/and from about 20 to 200 mg of metoprolol.

The beta-adrenergic receptor antagonists may be included in the levosimendan formulation or may be formulated separately as described above using principles well known in the art.

Salts of levosimendan may be prepared by known methods. Pharmaceutically acceptable salts are useful as active medicaments, however, preferred salts are the salts with alkali or alkaline earth metals.

Examples

Pharmaceutical examples.

Example 1. Concentrate solution for intravenous infusion

(a) levosimendan	2.5 mg/ml
(b) Kollidon PF12	10 mg/ml
(c) citric acid	2 mg/ml
(d) dehydrated ethanol	ad 1 ml (785 mg)

The concentrate solution was prepared by dissolving citric acid, Kollidon PF121 and levosimendan to dehydrated ethanol in the sterilized preparation vessel under stirring. The resulting bulk solution was filtered through a sterile filter (0.22 μm). The sterile filtered bulk solution was then aseptically filled into 8 ml and 10 ml injection vials (with 5 ml and 10 ml filling volumes) and closed with rubber closures.

The concentrate solution for intravenous infusion is diluted with an aqueous vehicle before use. Typically the concentrate solution is diluted with aqueous isotonic vehicles, such as 5 % glucose solution or 0.9 % NaCl solution so as to obtain an aqueous intravenous solution, wherein the amount of levosimendan is generally within the range of about 0.001 - 1.0 mg/ml, preferably about 0.01 – 0.1 mg/ml.

Example 2.

Hard gelatin capsule size 3	
Levosimendan	2.0 mg
Lactose	198 mg

The pharmaceutical preparation in the form of a capsule was prepared by mixing levosimendan with lactose and placing the powdery mixture in hard gelatin capsule.

Example 3.

Hard gelatin capsule size 3	
Metoprolol tartrate	100.0 mg
Lactose	198 mg

Experiments

Effect of the combination on the mortality of heart failure patients

A 6-hour infusion of levosimendan using a bolus of 6, 12 or 24 μg/kg and subsequent infusion of 0.1, 0.2 or 0.4 μg/kg/min was given to heart failure patients with or without concomitant use of a beta-blocker. The 72-hour, 14-day and 180 day mortality was measured. The results are shown in Table 1. It can be seen that the combination provided synergistic reduction in the mortality of the heart failure patients.

TABLE 1. The mortality of patients receiving levosimendan, a beta-blocker or a combination thereof.

	Received beta-blocker					Did not receive beta-blocker				
Event	Placebo (N=42)	LS 6+0.1 (N=43)	LS 12+0.2 (N=38)	LS 24+0.2 (N=32)	LS 24+0.4 (N=42)	Placebo (N=60)	LS 6+0.1 (N=60)	LS 12+0.2 (N=62)	LS 24+0.2 (N=67)	LS 24+0.4 (N=57)
	n (%)					n (%)				
72-hour mortality	3 (7.1%)	1 (2.3 %)	2 (5.3%)	0 (0.0%)	0 (0.0%)	7 (11.7%)	5 (8.3%)	1 (1.6%)	5 (7.5%)	5 (8.8%)
14-day mortality	6 (14.3%)	4 (9.3%)	4 (10.5%)	3 (9.4%)	2 (4.8%)	14 (23.3%)	9 (15.0%)	5 (8.1%)	10 (14.9%)	9 (15.8%)
180-day mortality	15 (35.7%)	13 (30.2%)	10 (26.3%)	12 (37.5%)	10 (23.8%)	31 (51.7%)	30 (50.0%)	25 (40.3%)	31 (46.3%)	26 (45.6%)

Claims

1. A medical product comprising, separately or together, as active ingredients levosimendan or a pharmaceutically acceptable salt thereof and a beta-adrenergic receptor antagonist as a combined preparation.

2. A pharmaceutical composition comprising as active ingredients levosimendan or a pharmaceutically acceptable salt thereof and a beta-adrenergic receptor antagonist.

3. Use of levosimendan or a pharmaceutically acceptable salt thereof and a beta-adrenergic receptor antagonist as active ingredients in the manufacture of a combined preparation for simultaneous, separate or sequential administration.

4. Use of levosimendan or a pharmaceutically acceptable salt thereof and a beta-adrenergic receptor antagonist as active ingredients in the manufacture of a medicament for reducing mortality of heart failure patients.

5. A method for the treatment of heart failure, said method comprising administering to a patient in need thereof levosimendan or a pharmaceutically acceptable salt thereof in combination with a beta-adrenergic receptor antagonist.

6. A method for reducing mortality of heart failure patients, said method comprising administering to a patient in need thereof levosimendan or a pharmaceutically acceptable salt thereof in combination with a beta-adrenergic receptor antagonist.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/FI 02/00606

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/501 A61K45/00 A61K31/403 A61K31/138 A61P9/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	JOHN G.F. CLELAND, MD, FRCP ET AL: "Levosimenda a new era for inodilator therapy for heart failure" CURRENT OPINION IN CARDIOLOGY, vol. 17, no. 3, May 2002 (2002-05), pages 257-265, XP002902743 page 257 page 260 page 264 ---	1-6
X	HEIMO HAIKALA ET AL: "The role of cAMP- and cGMP-dependent protein kinases in the cardiac actions of the new calcium sensitizer, levosimendan" CARDIOVASCULAR RESEARCH, vol. 34, no. 3, 1997, pages 536-546, XP002902480 page 541 -page 542 --- -/--	1-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2002	12 11. 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gerd Strandell/Eö

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national Application No
PCT/FI 02/00606

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KATALIN GYÖRGY ET AL: "Haemodynamic effects of intravenous levosimendan during oral metropol treatment in anesthetized dogs" JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY, vol. 29, no. 5, 1997, XP002902744 page A127, column Sa 81 ---	1-6
X	FIGGITT ET AL: "Levosimendan" DRUGS, vol. 61, no. 5, March 2001 (2001-03), pages 613-627, XP002902745 page 624 ---	1-6
X	A.LOCHNER ET AL: "Effect of a Calcium-Sensitizing agent, Levosimendan, on the Postcardioplegic Inotropic Response of the Myocardium " CARDIOVASCULAR DRUGS AND THERAPY, vol. 14, no. 3, 2000, pages 271-281, XP002901274 the whole document ---	1-6
X	NICOLAI GRUHN ET AL: "Coronary Vasorelaxant Effect of Levosimendan, a new inodilator with Calcium-sensitizing properties" JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, vol. 31, no. 5, 1998, pages 741-749, XP002902483 page 744 ---	1-6
X	MARA T. SLAWSKY, MD, PHD ET AL: "Acute Hemodynamic and Clinical Effects of Levosimendan in Patients with severe Heart Failure" CIRCULATION, vol. 102, no. 18, 2000, pages 2222-2227, XP002902746 page 2223 page 2226 ---	1-6
A	WO 98 58638 A (BRISTOW MICHAEL R) 30 December 1998 (1998-12-30) the whole document ---	1-6
A	WO 92 12135 A (ORION YHTYMAE OY) 23 July 1992 (1992-07-23) the whole document -----	1-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 02/00606

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 5, 6
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 5, 6

Claims 5, 6 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No
PCT/FI 02/00606

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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